ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

This application is a national stage entry under 35 U.S.C. §371 of PCT/IB98/01813, filed Nov. 13, 1998 which claims the benefit of U.S. Provisional Application Ser. No. 60/070,245, filed Dec. 31, 1997.

BACKGROUND OF THE INVENTION

This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac, arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

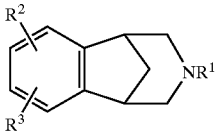
The compounds of this invention may also be used in combination with an antidepressant such as, for example, a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's Chorea or traumatic brain injury (TBI): in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD, stroke, Huntington's Chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD stroke, Huntington's Chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal antiinflammatory agents and estrogen-like therapy.

Other compounds that bind to neuronal nicotinic receptor sites are referred to in U.S. patent application Ser. No. 08/963,852, which was filed on Nov. 4, 1997 now U.S. Pat. No. 6,020,335. The foregoing application is owned in common with the present application, and is incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

This invention relates to aryl fused azapolycyclic compounds of the formula

(I)



R^1 is hydrogen, $(C_1–C_6)$alkyl, unconjugated $(C_3–C_6)$ alkenyl, benzyl, $XC(=O)R^{13}$ or $—CH_2CH_2—O—(C_1–C_4)$alkyl;

R^2 and R^3 are selected, independently, from hydrogen, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, hydroxy, nitro, amino, halo, cyano, $—SO_q(C_1–C_6)$alkyl wherein q is zero, one or two, $(C_1–C_6)$alkylamino-, $[(C_1–C_6)\text{alkyl}]_2$amino-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ $—XC(=O)R^{13}$, aryl-$(C_0–C_3)$alkyl- or aryl-$(C_0–C_3)$alkyl-O—, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0–C_3)$alkyl- or heteroaryl-$(C_0–C_3)$alkyl-O—, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and $X^2(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl-, wherein X^2 is absent or X^2 is $(C_1–C_6)$ alkylamino- or $[(C_1–C_6)\text{alkyl}]_2$amino-, and wherein the $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- moiety of said $X^2(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- may be optionally substituted with from two to seven fluonne atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-$(C_0–C_3)$alkyl- and said heteroaryl-$(C_0–C_3)$alkyl- may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from $(C_1–C_6)$alkyl optionally substituted with from one to seven fluonne atoms, $(C_1–C_6)$alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, hydroxy, nitro, cyano, amino, $(C_1–C_6)$-, $[(C_1–C_6)\text{alkyl}]_2$amino-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ and $—XC(=O)R^{13}$;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or a ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl-, wherein the total number of carbon atoms does not